Consistent Testing Terminology
Use Cases Workshop

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Consistent Testing Terminology Working Group
Use Case – Ovarian Cancer

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Use Case: Ovarian Cancer
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• American Cancer Society estimates for ovarian cancer in the United States for 2021 are:
  • ≈ 21,410 women will receive a new diagnosis of ovarian cancer
  • ≈ 13,770 women will die from ovarian cancer

• Over the past 20 years, BRCA1/BRCA2-related discoveries have profoundly changed our understanding & management of HBOC (hereditary breast and ovarian cancer). Patients with BRCA1/2 account for only approximately 15% of all women who have ovarian cancer

• Guidelines by NCCN (National Comprehensive Cancer Network), SGO (Society of Gynecologic Oncology), and ACOG (American College of Obstetricians and Gynecologists) all agree that anyone with a personal history of ovarian cancer should receive genetic counseling and testing (regardless of family history, age, or other risk factor).

• According to NCCN (2021):
  • In addition to mutations in BRCA1/2 and the genes associated with Lynch Syndrome (e.g., MLH1, MSH2, MSH6, PMS2) germline mutations in a variety of other cancer genes have been associated with increased risk of ovarian cancer (e.g., ATM, BRIP1, NBN, PALB2, STK11, RAD51C, RAD51D).
  • Studies testing large panels of genes have found that 3%-8% of patients with ovarian cancer carry mutations in genes other than BRCA1 and BRCA2 known to be associated with ovarian cancer susceptibility.
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NCCN Guidelines Version 1.2021
Ovarian Cancer/Fallopian Tube Cancer/
Primary Peritoneal Cancer

- Tumor molecular analyses as clinically indicated:
  - Next-generation sequencing (NGS) for \textit{BRCA1}/\textit{BRCA2} mutations, other somatic mutations (e.g., \textit{NTRK} gene fusions), and tumor mutational burden (TMB)
  - Additional testing (particularly for endometrioid carcinomas)
    - Immunohistochemistry (IHC) for DNA mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2)
    - Microsatellite instability (MSI) testing
  - In addition to \textit{BRCA1}/\textit{BRCA2} testing, other methods for evaluating HR deficiency status (i.e., genomic instability, loss of heterozygosity) can be considered.
  - Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.
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- Professional guidelines have been in place for 10+ years → and yet, research shows alarmingly low rates of genetic testing among OC survivors
- Last year, JCO (Journal of Clinical Oncology) published a baseline-setting study looking at genetic testing among rates among HBOC survivors → first population study of hereditary cancer genetic testing the U.S. with laboratory-confirmed testing results
- Study uses data from 83,000+ women from SEER cancer registries in California and Georgia and finds that, in 2013 and 2014:
  - → ≈ One-third of women with ovarian cancer underwent genetic testing for inherited BRCA1/2 mutations in compliance with guidelines
  - → Among patients who did receive genetic testing, 15% of ovarian cancer patients had “actionable” gene variants, meaning variants that might warrant changes in treatment, screening, and risk-reduction strategies
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- Presented at OCRA’s National Conference in September 2021 (300+ attendees)
- Heard a lot feedback about CTWG’s position w/ respect to CA-125 testing

→ Screenshots of pertinent slides

Where CA-125 Testing Fits In: What the Working Group decided (1/2)

- Traditionally we have viewed biomarker testing as “non-genetic” (& thus limited to things like CA-125) → BUT the rise of precision oncology and explosion of genetic/genomic testing has created some tension w/ this initial framing of the term “biomarker”
- The thought process in the paper is that the more salient distinction is not so much whether something is “genetic” or “non-genetic” but rather whether it originates from tumor tissue/malignancy or from the germline, as this has implications on treatment/familial risk
- We intentionally broadened the term “biomarker” to include BOTH tumor genetic testing results and more traditional biomarkers like CA-125.
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Where CA-125 Testing Fits In: What the Working Group decided (2/2)

- In application/use:
  - CA-125 testing can continue to be defined as “biomarker testing” — but to clarify, tag on “for CA-125” → “biomarker testing for CA-125”
  - When it comes to molecular tumor profiling, you could say “biomarker testing for molecular tumor characteristics” or “biomarker testing for molecular tumor profiling” to differentiate
  - Be sure you’re using “genetic testing for inherited mutation/cancer risk” solely to describe germline testing

Session title:
“How to Talk about Genetic Testing and Precision Oncology (& Why It’s So Confusing)”

Recommended session title:
"Understanding the Language of Cancer Testing: Biomarkers, Molecular Profiling, Genetic Testing."
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The sticky intersection between CA-125 testing & biomarker testing:

• CA-125 is a glycoprotein (sugar associated protein) commonly referred to as a "biomarker" or "tumor marker". The CA-125 provides information via a blood sample.

• It can assist in diagnosing and following ovarian cancer (& has multiple other clinical applications.

• Limitations → CA-125 is only elevated in 50% of women w/ early-stage ovarian cancer and 85% of women w/ advanced cancer
  • The CA-125 can be elevated in someone who does not have cancer.
  • The number does not correlate with the extent of disease.

• How is the CA-125 used in ovarian cancer?
  • It is used as a tool to detect changes in CA-125 levels. If elevated in a woman with ovarian cancer, it can represent disease status.
More on CA-125 in OC

• All women with ovarian cancer are given the CA125
• It is the most reliable and useful test for monitoring disease, however, for many women, it is not a good marker.
• Why do some gynecologic oncologists hate the CA-125? Evidence suggests that using the CA125 to diagnose recurrent disease sooner does not result in overall improved survival.
• Following the CA-125 more closely caused physicians to administer more chemotherapy without improving outcomes.
• The CA-125 test causes incredible anxiety in women with the disease
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• Make no mention of CA-125 tests in context of “biomarker testing”
  • OC population is already familiar with CA-125 tests and its application & discussing as part of “biomarker testing” in context of precision seemed to serve no real purpose and caused confusion.

• Gaps in education and awareness are considerable
  • OC patients/survivors who are in the know when it comes to “biomarker testing” are highly sophisticated in their knowledge and understanding.
  • BUT overall awareness and understanding is alarmingly low. As the JCO study found, nearly two-thirds of OC survivors haven’t received basic biomarker tested for inherited cancer risk in BRCA1/2 genes (in compliance with guidelines).
  • Geographic disparities are a particularly significant barrier for OC patient population.